Trends in Neurosciences

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REVIEWS

Review

Neuronal Regulation of Immunity in the Skin and Lungs

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The nervous and immune systems are classically studied as two separate entities. However, their interactions are crucial for maintaining barrier functions at tissues constantly exposed to the external environment. We focus here on the role of neuronal signaling in regulating the immune system at two major barriers: the skin and respiratory tract. Barrier tissues are heavily innervated by sensory and autonomic nerves, and are densely populated by resident immune cells, allowing rapid, coordinated responses to noxious stimuli, as well as to bacterial and fungal pathogens. Neural release of neurotransmitters and neuropeptides allows fast communication with immune cells and their recruitment. In addition to maintaining homeostasis and fighting infections, neuroimmune interactions are also implicated in several chronic inflammatory conditions such as atopic dermatitis (AD), chronic obstructive pulmonary disease (COPD), and asthma.

Highlights

Barrier tissues, such as the respiratory tract and skin, are major sites where swift communication between the peripheral nervous system and immune system occurs.

Recent insights have uncovered the molecular mechanisms by which nerves regulate tissue-resident immune cells, including innate lymphoid cells (ILCs) and mast cells.

Bacterial, fungal, and parasitic pathogens can directly signal to peripheral sensory nerves to induce neuroimmune interactions during infection of barrier tissues.

Neuroimmune interactions are involved in the exacerbation of many chronic inflammatory diseases, including asthma, COPD, AD, and psoriasis.

Immune cells in the lungs and skin can be positively or negatively modulated by the nervous system, depending on the type of peripheral sensory or autonomic nerves – representing neuroimmune regulatory switches.

The Nervous and Immune Systems: Allies Working under Duress

Our barrier tissues are under constant assault from a variety of environmental threats, including noxious chemicals, thermal changes, mechanical injury, and microbial pathogens. The nervous and immune systems are specifically armed to combat these assailants to maintain homeostasis and to coordinate host defense. Mammalian barrier tissues including the skin, lungs, and gut are innervated by the PNS that serves to detect stimuli, including harmful ones, to respond to them, and to regulate autonomic functions. The immune system responds to threats such as pathogens and irritants through antimicrobial mechanisms and clearance of damaged tissues. Whereas neural responses occur almost instantaneously, immune responses can take minutes to hours; the integration of these two systems through neuroimmune interactions creates a coordinated network that is ideally poised to preserve tissue integrity. Crosstalk between these systems is bidirectional because immune cells, nerves, and neurons are capable of responding to each other's products (e.g., neurotransmitter receptors on immune cells and cytokine receptors on neurons).

In this review we highlight studies investigating neuroimmune interactions that occur in the skin and the lungs (e.g., [1–3] for reviews on neuroimmune interactions in the gut). Neural-mediated control of immunity is a fast-moving area, and while we cannot encompass the whole breadth of the literature in this area, we highlight several recent advances with the goal of focusing on studies demonstrating mechanisms by which neurons control immunity by direct signaling to either tissue-resident cells or recruited immune cells. A key neuroimmune reflex we do not cover is the cholinergic anti-inflammatory reflex, which acts through the vagus nerve, splenic macrophages, and cholinergic T cells ([4] for review). We begin with an overview of general concepts of the role of neuroimmune interactions at barrier tissues. We next discuss the contribution of neuroimmune interactions in the skin, addressing its role in acute infection and chronic inflammatory diseases. The final section addresses neuroimmune interactions in the lung, with a focus on neural mediation of airway inflammation and chronic obstructive pulmonary disease (COPD).

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Neuroimmune Interactions at Barrier Tissues

Mammalian barrier tissues (e.g., skin, cornea, respiratory tract, gastrointestinal tract) interface with the environment, and must discern between innocuous and noxious stimuli, as well as maintaining homeostasis and integrity under changing conditions. The immune and nervous systems are tasked to carry out these essential functions. The immune system uses innate and adaptive mechanisms for host defense. The nervous system uses sensory neurons to induce protective nociceptive neural reflexes and the release of regulatory molecules and neurotransmitters that modulate inflammation to combat danger. Both systems coordinate their communication with epithelial cells to maintain barrier integrity to ward off threats. The crosstalk between the nervous and immune systems is a rapidly progressing field, and new studies highlight the importance of this communication within barrier sites.

PNS and the Immune System

The PNS consists of the somatosensory and motor branches. The motor branch is further divided into somatic and autonomic (sympathetic, parasympathetic, enteric) nervous systems. The somatosensory nervous system is responsible for mediating sensory functions, including touch, proprioception, and pain. Specialized subsets of somatosensory neurons include nociceptors and pruriceptors responsible for detecting noxious or itch-inducing stimuli, respectively. We focus attention on these neurons because their activation is typically coupled with immunity and inflammation. The autonomic system innervates a large number of tissues and serves to control involuntary activities: the sympathetic nervous system participates in the response of the body to stress, whereas the parasympathetic nervous system mostly maintains homeostasis [5]. All parts of the PNS coordinate responses to stressors and stimuli at host barrier tissues.

The skin and respiratory tract are densely populated by resident immune cells, including **mast cells** (see Glossary), dendritic cells (DCs), macrophages, innate lymphoid cells, and **γδ T cells** (Box 1). These cells have unique functions that are ideally poised to fight off pathogens and mediate wound healing at barrier surfaces. Neuroimmune interactions at these barrier tissues are an effective way to coordinate host defense.

Neurogenic Inflammation and Immune Modulation

'Neurogenic inflammation' was first termed following the observations that swelling, redness, and heat produced by chemical irritants are all dependent on local innervation, and that nerve stimulation leads to immediate vasodilation [6,7]. Neurogenic inflammation is mediated by sensory neuron release of neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P (SP), which act on the vasculature and induce mast cell degranulation to produce edema, vasodilation, and immune cell extravasation. In addition to neuropeptides, sensory neurons can also release ATP, glutamate, brain-derived neurotrophic factor (BDNF), and potassium, and receptors for many of these factors are expressed by multiple immune cells (DCs, T cells, neutrophils, and macrophages). Sensory neurons also form close associations with many resident tissue immune cells, including mast cells, innate lymphocytes, and **dermal dendritic cells (dDCs)** [5,8] (Box 1). Expression of acetylcholine (ACh) receptors (muscarinic and nicotinic) and norepinephrine (NE) receptors (including α and β adrenergic receptors) has been found on T cells, macrophages, DCs, natural killer (NK) cells, B cells, and other immune cells [9,10]. However, the role of ACh and NE signaling in directly mediating neurogenic inflammation is not well understood, and further research is needed [11].

Although the focus of this review is primarily on the modulation of immune cells by neurons, it is important to note that neuroimmune interactions are bidirectional. Neuronal cell bodies and their nerve endings have receptors that can respond to immune cell-derived cytokines, lipids,

Glossary

Antigen-presenting cells (APCs): cells that present antigens in complex with MHCs on their surfaces to T cells.
Bronchoalveolar lavage fluid (BALF): the fluid that results from a diagnostic procedure in which cells and other components from bronchial and alveolar spaces are obtained for various studies or diagnoses. BALF is typically analyzed to diagnose lung diseases.
Dermal dendritic cells (dDCs): APCs located in the skin dermal layer, which process and present antigens on their cell surface to T cells. dDCs act as messengers between the innate and the adaptive immune systems.
Eosinophils: granulocytic immune cells that are primarily responsible for combating extracellular parasites and are usually associated with allergic responses.
Innate lymphoid cells (ILCs): innate, tissue-resident immune cells that lack antigen receptors, and often have functions analogous to those of helper T cells, including protective immunity, regulation of homeostasis and inflammation, and tissue repair at barrier surfaces.
Leukotrienes: a family of eicosanoid inflammatory mediators produced by the oxidation of arachidonic acid that are released by leukocytes.
Mast cells: long-lived tissue-resident cells with an important role in many inflammatory settings, including host defense against parasitic infections and allergic reactions. Mast cells degranulate upon stimulation, and release important inflammatory mediators stored in granules, including cytokines, histamine, serotonin, and proteases.
γδ T cells: T cells that have T cell receptors with a γ chain and a δ chain, with the primary function of recognizing lipid antigens.
Type 2 T helper (T_H2) cells: orchestrate protective type 2 immune responses such as those targeting extracellular parasites or facilitating wound repair. However, T_H2 cells have also been found to contribute to several allergic and inflammatory diseases such as asthma.

Box 1. The Skin-Resident Innate Immune Cell Population

As one of the most densely innervated organs, the skin is an ideal environment for nerves to quickly communicate with resident immune cells (see Figure 1A in main text), coordinating essential functions such as host defense and homeostasis.

Macrophages are the most abundant hematopoietic skin immune cell population under steady-state conditions. These cells act as key sentinels in pathogen detection and tissue damage, utilizing proinflammatory cytokines and chemokines to attract other immune cells from circulation to sites of damage [19]. Macrophages constitutively express neurotrophins such as NGF and BDNF to maintain the growth and survival of neurons [70]. Macrophages can in turn respond to neural derived growth factors and to secreted neuropeptides, establishing crucial bidirectional crosstalk with neurons in the skin [71,72].

Skin mast cells are in close proximity to dermal vasculature. Mast cells are typically associated with T_H2 responses and allergic inflammation, although they have also been implicated in wound healing, pathogen defense, and contact hypersensitivity responses [19]. Mast cells are both potently activated by bioactive substances released by nerves (NGF, SP, etc.) and activate nerves, as discussed further in Box 2.

DCs can be classified into two major populations, Langerhans cells (LCs) and dermal DCs. LCs are located in the epidermis where their dendrites interweave with keratinocytes, enabling sampling of the environment. dDCs, located in the dermis, are a heterogeneous cell population with several subsets: $CD11b^+$, $CD103^+$, and $CD301b^+$ cell types. dDCs actively migrate throughout the dermis to survey the environment; they are important components of tolerance at steady-state, in immune regulation during skin damage, and in shaping the initial T cell response to skin pathogens [19]. dDCs can respond to nociceptive neurons and to the neuropeptide CGRP to drive skin inflammation in psoriasiform mouse models and in *C. albicans* infection [32,33].

Dermal γδ T cells comprise 50% of the total dermal T cell population in mice. These cells constitutively express IL-23 receptor, CCR6, and RORγT molecules (associated with T_H17 cells); upon stimulation by IL-23 or IL-1β, dermal γδ T cells produce IL-17A, which can augment neutrophil recruitment [19]. These cells are implicated in the pathogenesis of psoriasis and AD, as discussed below [32,33,37,38].

ILCs (discussed in Box 3) are grouped into three subsets based on their developmental requirements: ILC1s, ILC2s, and ILC3s. ILCs were originally described in mucosal tissues, such as the gut, but have also been identified in the skin: ILC2s were found to be enriched in human AD lesions, and ILC3s are recruited to imiquimod-induced psoriasiform lesions in mice [19,73].

growth factors, and proteases. This can serve to either amplify or dampen the neural response; in some cases sensitization of the neuron can also occur. Immune cells, by themselves, are capable of synthesizing and releasing 'neuromodulators' such as ACh and dopamine to further regulate both immune cells and neurons, creating complex neuroimmunomodulatory circuits [8].

Neuroimmune Interactions That Regulate Barrier Function

Barrier functions in the lungs and the skin are important in maintaining homeostasis and preventing infection. In mucosal surfaces such as the lung, CGRP, a neuropeptide from nociceptor neurons, has been found to regulate mucus production, which is a key aspect of barrier function [12,13]. Nociceptor neurons also mediate barrier leakiness from the lung parenchyma into the blood during bacterial infection [14]. Mechanisms such as tight junction regulation, antimicrobial peptide production, ciliary sweeping, and prevention of water loss are all important lung epithelial functions. However, not much is known about the neuroimmune interactions that regulate these aspects of lung barrier integrity.

In the skin, keratinocytes are epithelial cells that make up the stratified epidermis (Figure 1A), and as such are important cells in barrier function (regulation of water loss, antimicrobial peptide secretion). These cells can also contribute to many inflammatory skin conditions in which barrier functions are compromised. In addition, keratinocytes mediate itch through their release of thymic stromal lymphopoietin (TSLP), histamine, and endothelin 1 (ET-1) which activate surrounding pruriceptive nerves; itch promotes scratching and mechanical barrier disruption. The thickened scaly skin noted in inflammatory skin diseases can be the result of keratinocyte proliferation induced by neuropeptides (CGRP) and cytokines. Keratinocytes can also release nerve growth

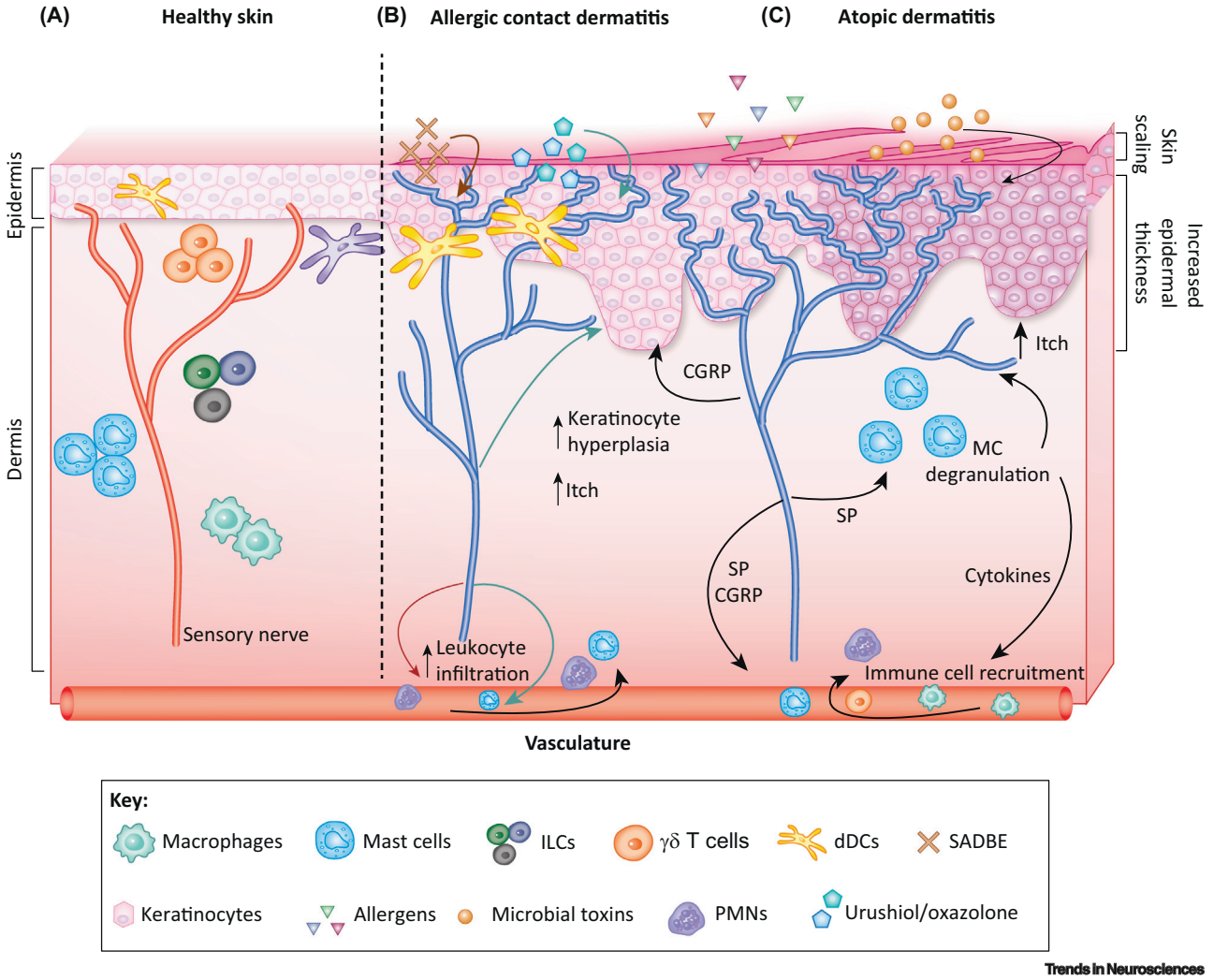

Figure 1. Neuronal Interactions with Immune Cells in Healthy Skin and in Dermatitis. (A) In healthy conditions, the epidermal layer is composed of tightly spaced keratinocytes which help to keep allergens, pathogens, and microbial toxins out. Skin-resident innate immune cells including dermal DCs (dDCs), γδ T cells, innate lymphoid cells (ILCs), and mast cells (MCs) are ideally poised to respond to signals communicated by surrounding sensory nerve fibers. (B) Allergic contact dermatitis (ACD) is a T cell-mediated, type IV hypersensitivity reaction induced by allergens/haptens that results in itchy and inflamed skin. The nociceptive ion channel TRPA1 was found to mediate both persistent itch and inflammation (edema, leukocyte infiltration, and keratinocyte hyperplasia) in mouse models of ACD driven by squaric acid dibutylester (SADBE), urushiol, or oxazolone [25,26]. Sensory nerves are thought to modulate the immune response by interacting with antigen-presenting cells (APCs) in these conditions [24]. (C) Atopic dermatitis (AD) is an allergic inflammatory skin condition that results in thickened scaly skin and impaired epidermal barrier function, allowing penetration of allergens and microbial toxins into the skin. Activated sensory nerves promote neurogenic inflammation (B,C) and secrete substance P (SP), which leads to degranulation of MCs that release histamine and other cytokines. This pruritogenic cocktail potentiates the itch–scratch cycle that is characteristic of AD, and also helps to further recruit immune cells to the inflamed area (darkened area surrounding each keratinocyte). Nerves also release calcitonin gene-related peptide (CGRP), which mediates keratinocyte hyperplasia, resulting in increased epidermal thickness (B,C) [29]. Keratinocytes also release nerve growth factor (NGF) (not shown), which leads to neuronal hyperinnervation and penetration of sensory nerves into the topmost layers of the skin, illustrated in the figure by the nerve endings (blue) extending through the spaces between keratinocytes into the topmost layers of the epidermis. Abbreviation: PMN, polymorphonuclear neutrophil.

factor (NGF) in response to SP and CGRP, mediating increased innervation and leakiness of the skin barrier [15]. Bidirectional keratinocyte–neuron interactions represent potent feedback loops that lead to exacerbation of chronic skin conditions, and also highlight the importance of barrier function for neuroimmune interactions in the skin.

Neuroimmune Interactions in the Skin

The skin is one of the largest organs in the human body, and its integrity is necessary for homeostasis, protecting barrier function, and combating invading dangers such as pathogens. The nerve fibers innervating the skin are in close proximity to skin structural and functional cells, including keratinocytes, fibroblasts, endothelial cells, Schwann cells, and resident immune cell populations [16]. The cutaneous sensory nerve fibers (CSNFs), which innervate both the dermal and epidermal layers, make up the majority of skin nerve fibers. CSNFs originate from the dorsal root ganglia (DRG) in the spinal cord or from the trigeminal ganglia. DRG neurons project afferent fibers to the skin of the trunk of the body; nerve signals from these fibers synapse onto the dorsal horn of the spinal cord where signals are transduced to the brainstem and thalamus. Trigeminal ganglia neurons innervate the skin of the head and face. CSNFs are responsible for sensory modalities including touch, thermosensation, mechanosensation, itch, and pain [15,17]. The autonomic nervous system innervating the skin is largely sympathetic, and makes up a small overall percentage of the nerve fibers. These nerves are restricted to the dermal layer and innervate hair follicles, blood vessels, lymphatic vessels, apocrine and eccrine glands, and erector pili muscles [17,18]. The resident immune population ensures both protection against pathogens and maintenance of tolerance against innocuous antigens (Box 1) [19]. The skin is densely innervated, and neuroimmune interactions are important for communication with the environment and for response to changes in it. Consistently, aberrant neuroimmune interactions can be the root of several inflammatory skin conditions. We next discuss the role of the nervous system in regulating acute neurogenic inflammation, pathogenic infection, and immunity in several skin diseases.

Acute Neurogenic Inflammation

Exposure of the skin to irritants, noxious stimuli, and even pathogens can promote neurogenic inflammation. Nociceptors release the neuropeptides CGRP and SP from nerve terminals that act on the vasculature and mast cells to induce vasodilation, edema, and immune cell recruitment. TRPA1 and CGRP were found to mediate the effects of vesicant-induced skin injury, edema, and inflammation [20]. TRPA1, as well as TRPV1, are important ion channels in inflammatory pain because they are activated downstream of cytokine signaling as well as by endogenous reactive species such as nitric oxide, peroxynitrite, and oxidized lipids [21]. In addition to acute neurogenic inflammation promoted by classically described irritants and noxious stimuli, this neural-driven process can be a component of inflammatory skin conditions, many of which are characterized by increased levels of SP and CGRP [22]. Recent work has shown that SP-driven activation of mast cells through MrgprB2 in mice and MrgprX2 in humans is a key molecular mechanism of neurogenic inflammation (discussed in Box 2).

Inflammatory Skin Diseases

Neuroimmune interactions contribute to the pathology of AD, psoriasis, and allergic contact dermatitis (ACD) (Figures 1B,C and 2A). Sensory neurons mediate both the itch associated with these disease conditions and neurogenic inflammation, leading to exacerbation and continuation of symptoms, as well as to denervation – resulting in amelioration of symptoms [22,23]. In these conditions, much is known about how the immune system communicates with sensory nerve endings to promote itch [TSLP, interleukin (IL-31), histamine], but far less is known about how these neurons control inflammation.

Allergic Contact Dermatitis

ACD is a T cell-mediated, type IV hypersensitivity reaction caused by various allergens/haptens, which results in itchy, inflamed skin. Cutaneous sensory nerves are hypothesized to modulate the immune response by interacting with **antigen-presenting cells (APCs)** [24]. It was recently determined that TRPV1 and TRPA1 contribute differentially to contact hypersensitization in a mouse

Box 2. Neural Regulation of Mast Cells

Mast cells are long-lived tissue-resident cells that are typically recognized for their role in IgE-mediated allergic inflammation. However, mast cells reach far beyond their classical role in allergies, and are capable of providing innate immune defense, regulation of adaptive immunity, and mediation of pain and itch. These functions are mediated through the rapid release of chemical mediators stored in preformed granules. As such, mast cells are present throughout the body, and a majority are found within connective tissues and barrier surfaces. Mast cell–nerve interactions were one of the earliest examples of neuroimmune relationships described, both anatomically and functionally. Several recent reviews highlight mast cell–neural relationships in depth [74–76].

SP is the most widely studied neuronal mediator of mast cell degranulation, and its 'traditional' receptor was identified as the neurokinin 1 receptor (NK1R). However, several studies have pointed to the inefficacy of NK1R antagonists in blocking SP-mediated activation of human mast cells [77]. Recent studies have identified that SP can also act through a class of receptors belonging to the Mas-related family of G-protein-coupled receptors (GPCRs) [78–82]. It has been found that basic secretagogs including SP, VIP, the canonical mast cell activator 48/40, as well as the antimicrobial peptide LL-37, are able to induce mouse mast cell degranulation both *in vivo* and *in vitro* through the receptor, MrgprB2, the ortholog of MrgprX2 in humans [76,78] (see Figure 3 in main text). The identification of this receptor will allow specific therapeutic targeting of MrgprX2 in chronic inflammatory and allergic diseases.

In another study, it was determined that mast cells release differently sized granules based on whether they are activated via IgE-independent or -dependent mechanisms. Interestingly, when SP activated mast cells via MrgprX2, degranulation was characterized by the rapid release of small spherical granules. By contrast, when mast cells where stimulated by IgE, degranulation resulted in larger and less spherical granules that not only took a longer time to be released but were of a different composition from those induced by SP (and other MrgprX2 agonists) [80]. This highlights the differences in IgE- versus SP-mediated activation of mast cells and in how different features of mast cell-dependent inflammation are elicited. Topical treatment with mastoparan, which activates connective tissue mast cells via MrgprX2, enhanced clearance of *S. aureus* from infected mouse skins and accelerated healing of dermonecrotic lesions [83]. Given the known role of SP to activate MrgprX2 receptors on mast cells, and the ability of bacterial pathogens to activate peptidergic neurons that express SP [36,39], it would be interesting to determine if nerve–mast cell interactions play a role in infection.

ACD model induced by squaric acid dibutylester (SADBE): SADBE directly activated both TRPV1 and TRPA1 channels on neurons to produce itch; only TRPV1 ion channels played a role in inflammation because ablation of $TRPV1^+$ neurons or genetic deficiency in TRPV1 led to increased inflammation [25]. By contrast, TRPA1 was necessary for mediating both itch and inflammation (edema, leukocyte infiltration, keratinocyte hyperplasia) in ACD mouse models using urushiol (poison ivy component) and oxazolone, whereas TRPV1 channels were not involved [26] (Figure 1B).

Atopic Dermatitis

AD is a chronic inflammatory skin condition characterized by chronic pruritus, thickened scaly skin, impaired epidermal barrier function, and a **type 2 T helper (T_H2) cell**-skewed allergic response. Chronic itch is a debilitating symptom of this condition, and the postulated mechanisms were previously highlighted [27], one being mast cell degranulation (Box 2). A stark feature of AD lesions is increased hyperinnervation and penetration of the sensory neurons into the epidermis, leading to increased itch and release of neuropeptides (Figure 1C). Lesions and blood samples from AD sufferers are high in SP and NGF which lead to keratinocyte hyperproliferation [27,28].

In an innervated skin model, where human AD skin samples were cocultured with porcine DRG, sensory nerves induced keratinocyte proliferation that was dependent on CGRP (Figure 1C). Isolated AD skin samples used in this model also showed increased innervation and neurite outgrowth, CGRP release, and epidermal thickening compared with healthy skin sample controls [29]. These studies show that neuroimmune interactions in the skin could be key underlying mechanisms related to both inflammation and skin thickening in AD.

Psoriasis

Psoriasis is a skin inflammatory disorder characterized by dysregulation in the IL-17/IL-23 axis, acanthosis, hyperkeratosis, and itch. Neuroimmune interactions mediate both induction of IL-23

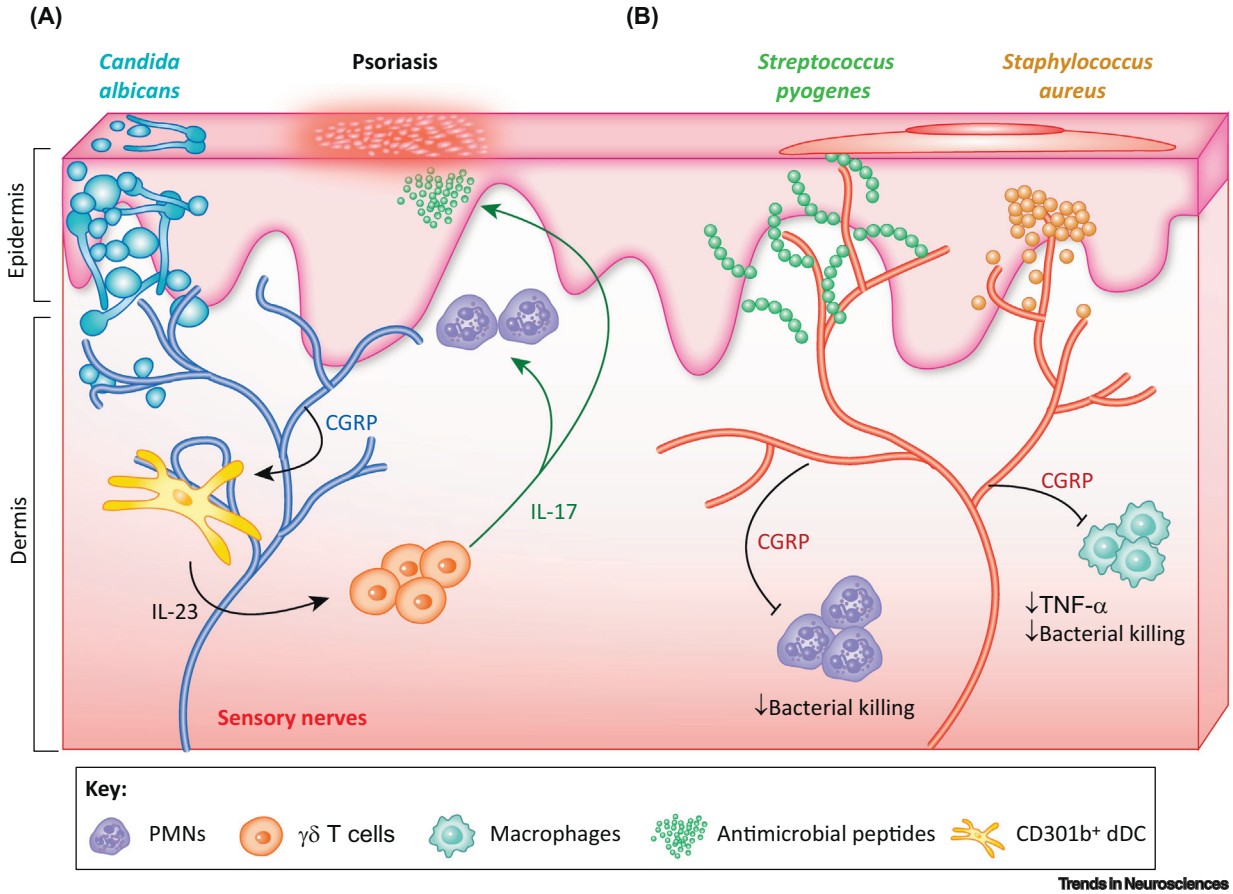

Figure 2. Neuroimmune Interactions in Skin Infection and Psoriasis. Several pathogens, such as *Candida albicans*, *Staphylococcus aureus*, and *Streptococcus pyogenes*, have been determined to interact with sensory nerves in the skin to drive neuroimmune modulation. Pathogenic activation of sensory nerves leads to release of neuropeptides that modulate immune cells during infection, affecting infection and disease outcome. (A) The pathogenic yeast, *C. albicans*, activates sensory nerves during epicutaneous infection to release the neuropeptide calcitonin gene-related peptide (CGRP), which augments the release of interleukin (IL)-23 from CD301b$^+$ dermal dendritic cells (dDCs). IL-23 then drives IL-17 release from γδ T cells, which mediates resistance against *C. albicans* by inducing polymorphonuclear neutrophil (PMN) recruitment and the expression of antimicrobial peptides (AMPs) [33]. In a mouse model of psoriasis, a similar neuroimmune interaction was found: sensory nerves mediate IL-23 release from dDCs which mediate IL-17 release by γδ T cells that contribute to psoriatic inflammation and plaque formation [32]. A similar neuroimmune mechanism operates during psoriasis-like inflammation. (B) *S. pyogenes* and *S. aureus* are bacterial pathogens that are known to cause painful and invasive skin infections such as abscesses, cellulitis, and necrotizing fasciitis. These pathogens directly activate sensory nerves via pore-forming toxins to produce pain and release CGRP from their nerve terminals. In *S. pyogenes* infection, CGRP prevents the recruitment of neutrophils (PMNs) and the subsequent killing of the bacteria, worsening infection outcome and bacterial clearance [35]. In *S. aureus* infection, nociceptor release of CGRP decreases both tumor necrosis factor (TNF)-α production from macrophages and lymph node hypertrophy, subsequently decreasing bacterial killing [36].

signaling and inflammatory lesion formation. The role of the sensory nervous system in psoriasiform skin inflammation was first shown by cutaneous denervation of a psoriasis mouse model [23]. When the skin was surgically axotomized in KC-Tie2 psoriasiform mice, acanthosis significantly improved, CD4$^+$ T cells and CD11c$^+$ DCs were decreased compared with the contralateral innervated side of the mouse. These characteristics were found to be largely dependent on CGRP and SP, suggesting targeting the nervous system as a treatment option for psoriasis. In a follow-up study, botulinum neurotoxin A (BoNT-A) was injected intradermally into KC-Tie2 mice [30]; this toxin cleaves SNAP25 and prevents local release of neuropeptides such as CGRP and SP. BoNT-A injection significantly improved both skin inflammation and epidermal hyperplasia. Small-scale human clinical trials have also shown the effectiveness of BoNT-A in improving plaque

psoriasis [31]. Using an imiquimod-driven model of psoriasis in mice, TRPV1$^+$ nerves were found to mediate IL-23 release by dDCs, which drive IL-17 expression by γδ T cells [32], thereby promoting psoriatic inflammation (Figure 2A). In all, sensory nerves play a major role in the propagation of inflammation in psoriasis, and it seems plausible that targeting neuroimmune interactions could offer a promising treatment approach.

Skin Infections

When fungal, bacterial, or viral pathogens breach the skin barrier, the immune system is recruited to the site of infection to combat the threat. Both host resistance and host tolerance mechanisms are regulated by the nervous system during infection. Pathogens have been shown to secrete molecules that directly interact with the sensory nervous system. Because neuroimmune interactions are essential for barrier function, one might conjecture that these sensory nerves actively recruit immune cells to the site of infection. This is true in the case of the fungal pathogen, *Candida albicans*, in an epicutaneous skin infection model [33]. It was found that *C. albicans* directly activates nociceptive sensory nerves to release CGRP, which in turn augments the release of IL-23 from dDCs; IL-23 subsequently drives IL-17 production by γδ T cells to mediate resistance against this fungus (Figure 2A). Therefore, nociceptors are necessary for successful protection against *C. albicans* skin infection. Recent work has also shown that nociceptors boost the resolution of osteoinflammation in the bone caused by *C. albicans* by suppressing β-glucan-induced inflammation and osteoclast multinucleation through CGRP signaling [34].

Activation of sensory nerves can also potently suppress the recruitment and function of immune cells during skin infection. In a recent study, the pathogen responsible for necrotizing fasciitis, *Streptococcus pyogenes*, was found to activate TRPV1$^+$ nerves, thereby promoting the secretion of CGRP. CGRP in turn prevented the recruitment of neutrophils and subsequent *S. pyogenes* opsonophagocytic killing, partly by reducing myeloperoxidase (MPO) activity (Figure 2B) [35]. When mice were depleted in the TRPV1 subset of neurons, infection severity decreased and neutrophil recruitment to the site of infection was increased. Blockade of neuronal signaling using botulinum neurotoxin or the CGRP receptor antagonist, BIBN4096, led to significantly improved neutrophil recruitment and infection outcome. Similarly, when a large portion of nociceptive neurons were depleted using *Nav1.8–cre* lineage ablation in mice, monocyte recruitment and lymphadenopathy increased in a *Staphylococcus aureus* subcutaneous infection model; CGRP also decreased tumor necrosis factor (TNF)-α production from macrophages (Figure 2B) [36].

Neuroimmune signaling may be finely tuned to the pathogen, and even to the specific area of the skin that is affected. For example, it is possible that itch-mediating pruriceptor neurons that largely innervate the epidermis could respond to distinct pathogens instead of deeper tissue-innervating pain-mediating nociceptor neurons. *S. aureus* subcutaneous infection causes painful abscesses, whereas epicutaneous infection can contribute to chronic itch. Skin colonization by *S. aureus* affects >90% of AD patients, often exacerbating this itch-inducing condition. Epicutaneous infection with *S. aureus* leads to inflammation via keratinocyte release of IL-36 that promotes IL-17 production from γδ T cells [37,38]. Our laboratory has determined that *S. aureus* is capable of interacting with nociceptor sensory nerves to produce pain during subcutaneous infections by secreting bacterial pore-forming toxins [36,39]. However, the question remains whether this pathogen can directly activate pruriceptor nerves at the barrier surface to induce itch and modulate neuroimmune interactions.

In addition to producing pain or itch during infection, other pathogens silence pain. Determining the molecular mechanisms involved could lead to the development of novel analgesics. The pathogen *Mycobacterium ulcerans* produces extensive skin lesions known as Buruli ulcers that are characteristically painless. Originally it was believed that this analgesia was due to nerve damage;

however, a recent study showed that mycolactone, an essential polyketide toxin of this pathogen, interacts with angiotensin 2 receptors (AT2Rs) to hyperpolarize sensory nerves through the opening of TRAAK potassium channels [40,41]. Because mycolactone can diffuse throughout the body, another study suggested that part of this analgesic effect may be due to the decreased neuroinflammation induced by this molecule [42]. However, in this study the effects of mycolactone were tested by intrathecal delivery; whether mycolactone would reach the CNS or DRG during *M. ulcerans* skin infection is currently unclear. More recently, AT2R was detected on macrophages infiltrating nerve injury sites, and these $AT2R^+$ macrophages were necessary for the development of chronic neuropathic pain in peripheral tissues [43]. It would be interesting to determine whether *M. ulcerans* also acts on $AT2R^+$ macrophages to block pain.

Sympathetic Nervous System and Skin Immunity

The sympathetic nervous system innervates the hair follicles and sebaceous glands in the skin, regulating stem cell regeneration, but its role in neuroimmune interactions is not as well studied. Sympathetic nerves can have important roles in immunity, especially because chronic 'stress' is known to exacerbate inflammatory skin diseases such as AD [44]. Using a heterotypic chronic stress model in rats, β_2-adrenergic receptors were found to mediate increased itch hypersensitivity after administration of 5-hydroxytryptamine through the release of proinflammatory factors (TNF-α and IL-1β) [45].

Neuroimmune Interactions in the Respiratory Tract

Gas exchange with the external atmosphere occurs in the lungs. During respiration, the lung epithelial surface acts as a barrier surface that comes into direct contact with the environment [46]. With the constant risk of exposure to harmful substances, detection of these potential dangers and pulmonary immunity against them are important. Nerves are therefore crucial in quickly detecting harmful substances to coordinate immune responses, which ultimately can limit the magnitude of lung infection and help to resolve inflammation. Similarly to the skin, resident immune cells are also important for the quick response to barrier insult; these include macrophages, where a subpopulation was recently described to be closely associated with nerves in the lungs [47]. We highlight recent studies showing roles for lung-innervating neurons in regulating immune cell function in asthma, COPD, and lung infections.

Sensory nerve lung innervation largely originates from vagal afferents whose cell bodies reside in the nodose and jugular ganglia; remaining sensory nerve innervation comes from the DRG [48]. Nociceptive afferent nerve endings are located in the lung parenchyma and near the airways; this poises them to detect noxious stimuli such as allergens, irritants, and pathogens that are contained in inhaled air, and expel them through cough [5]. Sympathetic nerve innervation originates from the upper six thoracic segments of the spinal cord; these synapse with the sympathetic ganglia, and postganglionic fibers then innervate the lung. The cholinergic parasympathetic nerves originate from the vagal nuclei in the medulla; the superior and recurrent laryngeal vagal nerve branches synapse at the parasympathetic ganglia to innervate the airways [48] (Figure 3). The sympathetic nervous system controls bronchodilation and mucous production, whereas the parasympathetic nervous system controls bronchoconstriction. Regulation of oxygen and carbon dioxide levels, as well as neural reflexes such as coughing, results from these systems. The necessity of neuroimmune interactions in the lung was shown through vagotomy – which worsens lung infections, inflammation, and injury while increasing proinflammatory cytokine levels in the circulation in an *Escherichia coli*-induced acute lung injury model [49].

Sensory Neuron–Immune Interactions in Asthma and Airway Inflammation

Neuroimmune interactions have been extensively studied in asthma, an airway allergic reaction characterized by airway hyper-responsiveness and inflammation [50]. Nociceptor sensory nerves

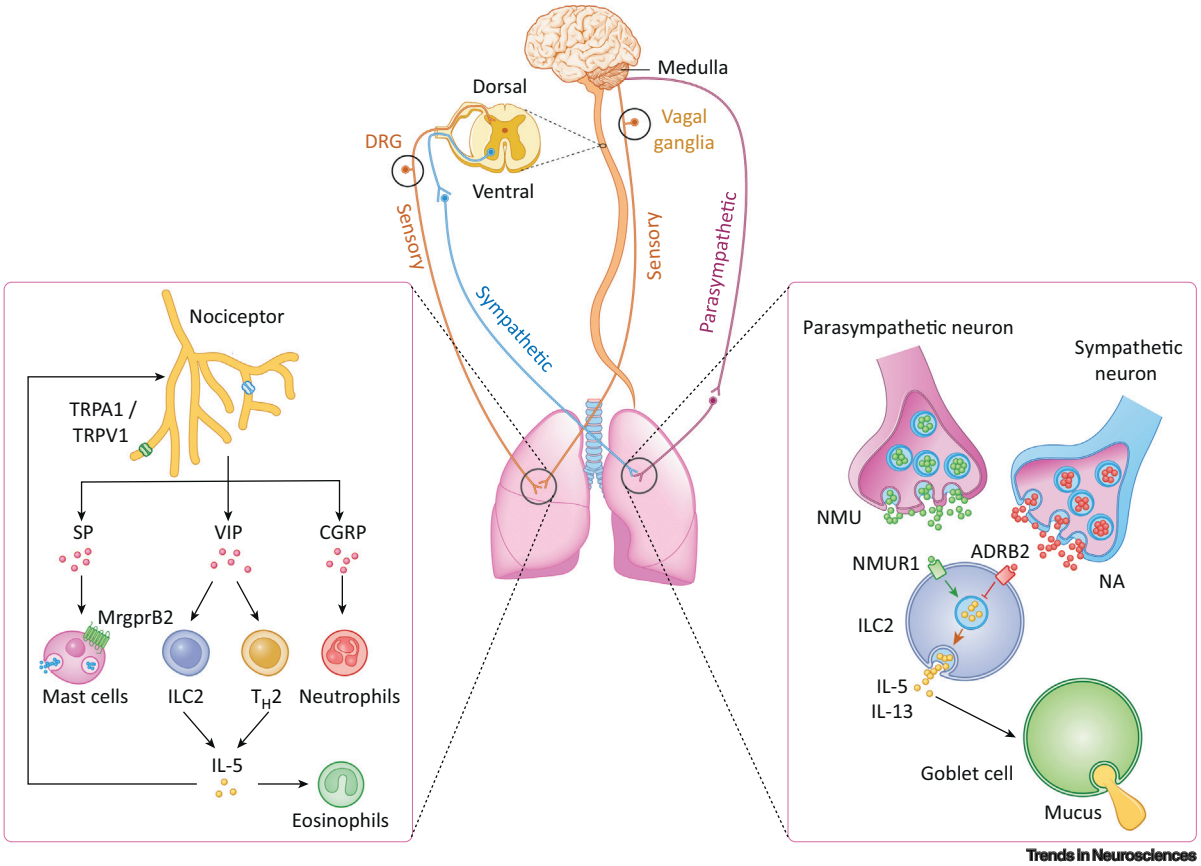

Figure 3. Neuroimmune Interactions in the Lungs. The lungs (center) are innervated by the parasympathetic, sympathetic, and sensory components of the peripheral nervous system. Parasympathetic nerves which originate in the medulla travel to the lungs via the vagus nerve. Sympathetic nerves originate in the ventral horn of the spinal cord. Nociceptive sensory nerves either innervate the lungs via the vagus nerve from the nodose and jugular ganglia or from the dorsal root ganglion located in the spinal cord. (Left) Lung-innervating nociceptor neurons can be activated by TRPV1 and/or TRPA1 stimulation in response to a variety of stimulants such as chemicals and irritants. Release of the neuropeptide calcitonin gene-related peptide (CGRP) can inhibit neutrophil recruitment and surveillance [14,67,68], whereas vasoactive intestinal peptide (VIP) activates innate lymphoid type 2 cells (ILC2s) [84] and type 2 T helper (T_H2) cells [54]. T_H2 cells produce interleukin (IL)-5, a potent activator of eosinophils. Substance P (SP) binds to Mas-related G protein-coupled receptor member B2 (MrgprB2) on mouse mast cells [78], resulting in their degranulation and thus the release of histamine and other cytokines. (Right) Lung-innervating autonomic neurons modulate ILC2 function. Parasympathetic nerves release neuromedin U (NMU) which acts on NMU receptor 1 (NMUR1) expressed on ILC2s to trigger the release of IL-5 and IL-13. IL-5 and IL-13 can then act on goblet cells to promote mucus release [58,59,61]. Noradrenaline (NA) release from sympathetic nerves, which binds to β2-adrenoreceptor (ADRB2) on ILC2s, inhibits the release of these cytokines [60]. Abbreviation: DRG, dorsal root ganglia.

were shown to play an important role in the etiology of asthma in several studies utilizing ovalbumin (OVA)-sensitization mouse models, as discussed here. The nociceptive TRPA1 ion channel was first shown to play a crucial role in driving immune cell cytokine production and airway hyper-reactivity in this model [51]. Treatment of mice with capsaicin to induce loss of $TRPV1^+$ nociceptor neurons reduced both **eosinophil** infiltration and inflammation in OVA-induced airway inflammation [52]. Targeted genetic ablation of $TRPV1^+$ neurons in the nodose/jugular vagal ganglia, which provide major sensory innervation to the lungs, or silencing these neurons using a tetanus toxin reporter, was shown to significantly reduce bronchial hyper-responsiveness in the OVA mouse model [53]. When $NaV1.8^+$ nociceptors were genetically ablated or pharmacologically inhibited using the membrane-impermeant sodium channel blocker, QX-314, immune cell infiltration and bronchial hyper-responsiveness were reduced [54]. Sensory neuron expression of vasoactive intestinal peptide (VIP) was thought to contribute to activation of both $CD4^+$ T_H2

cells (Figure 3, left) and type 2 **innate lymphoid cells (ILC2s)** (Box 3) [54]. Coexposure to the pollutants PM2.5 and formaldehyde in the OVA mouse model of asthma exacerbated the activation of TRPV1 signaling pathways, leading to increased inflammation. Treatment with capsazepine (TRPV1 antagonist) decreased both neuropeptide production and oxidative stress [50].

Recent studies have shown a role for TRP channels in other models of asthma. TRPA1 and TRPV1 channels were also shown to mediate the induction of airway hyper-reactivity (AHR) caused by TDI (toluene-2,4-diisocyanate), a model known to induce immune-mediated asthma in mice. Mast cells were also shown to be crucial for AHR, and the authors speculated about whether degranulation of mast cells induced by SP was a key mechanism; however, follow-up studies will be necessary to confirm the neuroimmune interaction occurring in this context [55]. Nerves and mast cells have been shown to interact closely in several tissues, including the skin and lungs. Recent work has uncovered a crucial role for the MrgprX2 receptor in human mast cells (and MrgprB2 in mouse mast cells) in detecting SP released from nerves to mediate mast cell degranulation (Figure 3 left, and Box 2).

Autonomic Neuroimmune Interactions in Asthma and Airway Inflammation

The parasympathetic nervous system interacts with immune cells through the action of ACh on muscarinic receptors to induce airway inflammation. Activation of muscarinic receptors promotes

Box 3. Neural Regulation of Innate Lymphoid Cells

ILCs are a heterogeneous population of cells that are diverse in their cytokine production, effector functions, and tissue locations. ILCs characteristically do not express T cell receptors or B cell receptors, and have characteristics that resemble innate lymphocytes. Based on their developmental requirements, and cytokine and cell-surface marker expression, ILCs are grouped into three populations: ILC1s, ILC2s, and ILC3s [73].

Recent work has shown that neurons closely interact with ILC2s, although it is likely that other major interactions occur between neurons and the other ILC subtypes. ILC2s are potent sources of cytokines that contribute to the type 2 inflammatory response; in particular, ILC2s are associated with wound healing, allergy, and parasitic worm infection at mucosal surfaces. VIP was first shown to interact through VPAC2 receptors expressed on ILC2s in the gut, suggesting that neural–ILC interactions could take place at mucosal surfaces [84] (see Figure 3 in main text). Further studies indicated a role for NMU, a neuropeptide produced by cholinergic neurons, in the regulation of ILC2s; both NMU^+ nerve fibers and ILCs are in close proximity with each other in the lungs, where ILC2s selectively express NMU receptor 1 (NMUR1). Activation of ILC2s by NMU induced rapid expression of type 2 inflammatory cytokines (IL-5 and IL-13) which act on goblet cells to induce goblet cell hyperplasia and mucous production (see Figure 3 in main text); this mechanism of neural-driven ILC2 activation was crucial for mediating both airway hypersensitivity and inflammation following exposure of mice to allergens and parasitic worms [58,59,61]. By contrast, ILC2s are inhibited by the sympathetic nervous system through the β_2AR. Catecholaminergic neurons, which secrete molecules such as norepinephrine/noradrenaline (which bind to β_2AR), were recently shown to act as off-switches that dampen ILC2 responses. β_2AR deficiency resulted in exaggerated type 2 inflammation and ILC2 responses in the lungs; β_2AR agonist treatment led to reduced inflammation and impaired ILC2 responses [60] (see Figure 3 in main text). These recent studies show that there are multiple tracks by which the nervous system is poised to trigger barrier protection programs that can either switch on or off ILC2 responses.

Pulmonary neuroendocrine cells (PNECs) are rare airway epithelial cells with poorly understood functions. In rodents, these cells can form highly innervated, clustered neuroepithelial bodies. In an *Ascl1* mutant mouse model, which prevents PNEC formation in airway epithelia, ILC2s and goblet cell hyperplasia were both decreased under allergic asthma conditions. PNEC release of CGRP and GABA was determined to be necessary for ILC2 cytokine expression and goblet cell hyperplasia, respectively [67].

All three subtypes of ILCs have been found in the skin under steady-state conditions [85]. The importance of skin ILCs to the pathology of inflammatory skin conditions is only emerging, and neural–ILC connections have yet to be established. Skin ILC2s in AD were found to be regulated by TSLP, IL-25, and IL-33, all of which are upregulated in human AD lesions [73,86]. Psoriasis is associated with epidermal thickening (IL-22) and neutrophilic invasion (IL-17A/F); these cytokines were found to be largely produced by skin populations of ILC3s and γδ T cells rather than by T_H17 cells [87]. Given the strong neural contribution to both AD and psoriasis, it is possible that skin ILC subtypes are also regulated by nerves during inflammation.

the release of several cytokines and growth factors that are involved in asthma and COPD pathology. During allergic airway inflammation, epithelial damage promotes reflex mechanisms by exposing vagal nerve endings in the submucosa to the airway lumen, leading to ACh release from vagal parasympathetic neurons. M1 receptor (M1R) activation on epithelial cells can induce **leukotriene** B4 (LTB4) release, stimulating neutrophil, eosinophil, and monocyte chemotaxis [56]. Muscarinic 3 receptors (M3Rs) on structural cells in the lung also play a proinflammatory role; genetic ablation of M3R prevents neutrophilic airway inflammation in response to cigarette smoke exposure [57]. Muscarinic agonists can also act on macrophage M3R and M5R, promoting both their chemotaxis and release of LTB4 [56] in the lung. Recent work also highlights a key interaction of neurons with ILCs at mucosal surfaces (Box 3). ILC2s were found to express high levels of the neuropeptide receptor NMUR1. Neuromedin U (NMU), a neuropeptide, whose main source is cholinergic neurons, acts on the NMUR1 receptor to increase ILC2 proliferation and cytokine production during helminth and allergen challenge in both the lungs and the gut [58,59,61].

The sympathetic nervous system also modulates immune cells via noradrenaline-mediated activation of β2 adrenergic receptors (β_2AR) on ILCs and other immune cells [60,62–64]. β_2AR agonists are potent smooth muscle relaxers and can inhibit immune cell recruitment, activation, cytokine release, and their survival [63]. Paradoxically, β_2AR is also essential to induce a full asthma phenotype in mice because its activation on airway epithelial cells was necessary for inducing the cardinal features of asthma (inflammation, mucus production, and airway hyper-responsiveness) by regulating responses to IL-13 [64]. By contrast, β_2AR signaling inhibited activation of ILC2s in mouse models of asthma and inflammation, leading to dampening of key cytokines that drive airway inflammation [60]. In this way, the autonomic nervous system has distinct mechanisms by which it can control airway immunity and responsiveness.

Neuroimmune Interactions during COPD

COPD, a progressive disease involving pulmonary inflammation and obstruction, causes an increase in M1R and M3R expression in airway structural and sputum cells as a result of prolonged ACh release. In a mouse model of COPD caused by exposure to cigarette smoke, treatment with tiotropium, a long-acting muscarinic antagonist, decreased the levels of several inflammatory mediators (IL-6, TNF-α, LTB4) in the lungs [65]. In a rat model of resistive breathing (RB) that models severe COPD, tiotropium used before induction of RB reduced inflammatory infiltrates and attenuated lung injury and protein in **bronchoalveolar lavage fluid (BALF)** [66] compared with untreated rats. Further studies will be necessary to clarify the neuroimmune interactions in COPD.

Neuroimmune Interactions during Lung Infections

Bacteria, viruses, and fungi cause lung inflammation, irritation (cough), and AHR. Neuroimmune interactions at the lung/air barrier surface also occur during lung infections. During *S. aureus*-induced lethal bacterial pneumonia, TRPV1$^+$ nociceptors suppress immunity against this bacterium through CGRP release; this neuropeptide decreases the recruitment and surveillance of neutrophils that mediate killing of bacterial pathogens (Figure 3, left). As a result, nociceptor ablation increases survival, cytokine induction, and bacterial clearance in the lung [14]. Of note, CGRP is also expressed by pulmonary neuroendocrine cells (PNECs) in the lung in addition to sensory nerves. PNECs were found to play a role in regulating immune cell recruitment in the lungs [67,68]. Future work will be required to dissociate neural- versus PNEC-derived CGRP in different lung infections.

In influenza A viral infections, the sympathetic nervous system increases proinflammatory cytokines and exacerbates infection. Peripheral sympathectomy (using 6-hydroxydopamine) reduced

morbidity and mortality in lethal influenza A virus-induced pneumonia owing to decreased influx of monocytes, neutrophils, and NK cells, as well as to a diminished innate cytokine response [69].

Concluding Remarks and Future Perspectives

Barrier tissues including the skin and respiratory tract are constantly exposed to the outside environment as well as to threats to our health and internal homeostasis. These tissues are therefore heavily innervated, and the nervous system is poised to quickly detect insults and in turn recruit the immune system and communicate with it. This establishes crucial neuroimmune crosstalk that is necessary for maintenance of barrier function and host defense. Although there are some shared features between the lungs and skin in their overall protection strategy, it is not currently clear whether there are specific shared mechanisms between the lungs and the skin. Neuropeptide regulation of immune cells and neurogenic inflammation seem to be commonalities between the two barriers; however, specific similarities and differences in their functionalities are currently speculative. Moreover, the skin directly interfaces with the external environment, whereas the lung is a mucosal tissue, and each of the two barriers has distinct subtypes of immune cells and epithelial makeup. It will be interesting to see whether parallels in neuroimmune interactions between the two barrier sites emerge as the field progresses.

There are still many remaining questions to be answered (see Outstanding Questions) concerning neuroimmunity in the skin and respiratory tract, including the logic of why particular neurotransmitters and neuropeptides mediate immune cell proliferation or activation, whereas others suppress immune cell function. The role of neuroimmune interactions in barrier surfaces during development is another important area for future investigations. Defining the key molecular mechanisms underlying the communication between the immune and nervous systems could lead to novel therapeutic targets. Given that neurologists have already developed highly specific pharmacologic agonists and antagonists for many neurotransmitter receptors to treat neurologic diseases, these drugs may be repurposed to modulate neuroimmune signaling in the skin or respiratory tract, and this could open up exciting opportunities for possible treatments of inflammatory and infectious diseases.

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Outstanding Questions

What is the integrative logic of neural control of immunity in barrier surfaces? Although it is well established that both the sensory and autonomic branches of the peripheral nervous system control immunity, the biological advantages for why some peripheral neural signals activate immune responses whereas others suppress them remains unclear. Understanding how neural signals are integrated by the immune system as a whole and within individual cell types is an important future research topic.

Can neural-targeted therapies be a viable option to treat inflammatory diseases? Chronic inflammatory diseases such as rheumatoid arthritis, asthma, AD, and colitis are mostly treated with immune-targeted drugs. What are the effects of individually treating the immune or neural components of these diseases? Would a two-pronged approach targeting both systems alleviate immunopathology more quickly?

Can information about the pathogens impact on neurons be used to develop novel approaches to treat infection? Does the location of pathogen invasion affect neuroimmune interactions (i.e., the types of immune cells that are recruited, the neuroimmune modulation mechanism)? Does the same pathogen differentially induce neuroimmune interactions at different barrier surfaces (i.e., gut, lungs, skin)? These questions could lend insight into future treatments because antibiotic-resistant pathogens are on the rise.

How does the microbiota impact neuroimmune interactions at barrier tissues? Emerging evidence shows that both microbes and pathogens regulate neural function. Gut, lung, or skin commensal microbes may have a major impact on neuroimmune signaling.

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